REMARKS

The term "epithelial" in the terminology of "corneal epithelial disorder" which was added to claims 1 to 4, 6 to 8 and 11 to 13 is supported by the paragraph bridging pages 1 and 2 of the specification.

Enclosed is a MARKED-UP VERSION OF THE AMENDMENTS TO THE CLAIMS.

New claims 14 to 18 are supported in the specification on page 7, lines 14 to 19.

Claims 1 to 13 were rejected under 35 USC 102 as being anticipated by Liliom et al., Am. Phys. Soc., 274, C1065-C1074 (1998).

Liliom et al. tested the effect of oleyl lysophosphatidic acid ("LPA") for promoting proliferation for only keratocytes. The present claims, however, relate to a therapeutic agent composition for a corneal epithelial disorder and to a method for treating a corneal epithelial disease. The present invention does not relate to corneal disorders of keratocytes.

Thus all of the disorders recited in applicants' claims 4 to 7 and 11 to 13 of corneal ulcer, corneal erosion, keratitis and dry eye are symptoms caused by corneal epithelial defects.

Although Liliom et al. tested the effect of oleyl lysophosphatidic acid ("LPA") for promoting proliferation for keratocytes, they did not test an effect of LPA on corneal epithelial cells (see columns 1 and 17). The presently claimed invention is novel, since Liliom et al. do not describe an effect of LPA for (i) promoting proliferation for corneal epithelial cells and (ii) therapeutic effects on corneal epithelial disorders.

The cornea mainly consists of an epithelial layer, a stromal layer and an endothelial layer. The thickness of the epithelial layer is about one tenth as thick as that of the cornea, whereas the thickness of the stromal layer is about nine tenths as thick as that of the cornea. The corneal epithelial layer protects the eyeball from external stimulation as a barrier to shut-off the corneal stromal layer from the outside of eyeballs, whereas the corneal stromal layer participates in maintenance of water in the cornea and greatly affects transparency of the cornea. The corneal epithelial layer has a five to six-layer structure of corneal epithelial cells, and the cells are changed in a turnover of about one week. On the other hand, the corneal stromal layer has keratocytes, which are mesenchyme cells, scattered in the stromal layer consisting of an extracellular matrix, and it is said that a turnover of the keratocytes is two to three years. Accordingly, corneal epithelial cells are substantially different from keratocytes in structure, function, etc.

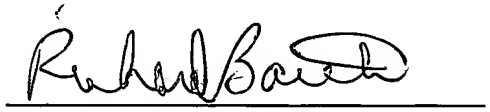
Attached is a copy of Steven E. Wilson et al., Investigative Ophthalmology & Visual Science, July 1993, Vol. 34, No. 8, 2554-2561, which describes on pages 2554 and 2555 that EGF (epidermal growth factor) has effects for promoting the proliferation for all of the epithelial cells, the keratocytes and endothelial cells of the cornea (see Figs. 8 and 9). On the other hand, it is shown that HGF (hepatocyte growth factor) and KGF (keratinocyte growth factor) have effects for promoting the proliferation for the epithelial cells and the endothelial cells, but have no effect for promoting the proliferation for the keratocytes. Since the epithelial cells, the keratocytes and the endothelial cells of the cornea differ in structure and role, it cannot be predicted whether or not the compounds having an effect of activating Rho of the present invention would have an effect for promoting the proliferation of the corneal epithelial cells, until pharmacological tests are carried out. The present invention is therefore not obvious over Liliom et al.

It is therefore respectfully submitted that applicants' claimed invention is not anticipated and is not rendered obvious by Liliom et al.

Reconsideration is requested. Allowance is solicited.

If the Examiner has any comments, questions, objections or recommendations, the Examiner is invited to telephone the undersigned at the telephone number given below for prompt action.

Respectfully submitted,



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Enc.: (1) MARKED-UP VERSION OF THE AMENDMENTS TO THE CLAIMS
(2) copy of Steven E. Wilson et al., Investigative Ophthalmology & Visual Science, July 1993, Vol. 34, No. 8, pages 2554-2561

MARKED-UP VERSION OF THE AMENDMENTS TO THE CLAIMS (SERIAL NO. 09/869,949)

1. (Twice Amended) A therapeutic agent composition for a corneal epithelial disorder comprising a compound having an effect of activating Rho as an active ingredient and a pharmacological carrier.

2. (Twice Amended) The therapeutic agent composition for the corneal epithelial disorder as claimed in claim 1, wherein the compound having the effect of activating Rho is lysophosphatidic acid or an acyl derivative thereof.

3. (Twice Amended) The therapeutic agent composition for the corneal epithelial disorder as claimed in claim 2, wherein said compound having the effect of activating Rho is [oleoyl] oleyl lysophosphatidic acid.

4. (Twice Amended) The therapeutic agent composition for the corneal epithelial disorder as claimed in claim 1, wherein the corneal disorder is corneal ulcer, corneal erosion, keratitis or dry eye.

6. (Amended) The therapeutic agent composition for the corneal epithelial disorder as claimed in claim 2, wherein the

corneal disorder is corneal ulcer, corneal erosion, keratitis or dry eye.

7. (Amended) The therapeutic agent composition for the corneal epithelial disorder as claimed in claim 3, wherein the corneal disorder is corneal ulcer, corneal erosion, keratitis or dry eye.

8. (Amended) A method of treating a corneal epithelial disorder comprising administering to a patient in need thereof a therapeutically effective amount of a compound having an effect of activating Rho.

11. (Amended) The method as claimed in claim 8, wherein the corneal epithelial disorder is corneal ulcer, corneal erosion, keratitis or dry eye.

12. (Amended) The method as claimed in claim 9, wherein the corneal epithelial disorder is corneal ulcer, corneal erosion, keratitis or dry eye.

13. (Amended) The method as claimed in claim 10, wherein the corneal epithelial disorder is corneal ulcer, corneal erosion, keratitis or dry eye.